II. REMARKS

Formal Matters

Claims 31, 35-38, 40-47, 51, 52, 59, 60, 62 and 64 are pending after entry of the amendments set forth herein.

Claims 31, 35-38, 41-47, 51, 52, 56, 59, 60, 62, 63, and 65 were examined and were rejected. Claims 40 and 64 were withdrawn from consideration.

Claims 31, 38, 60, and 62 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. The amendments to claims 38 and 62 are merely editorial in nature; as such, no new matter is added by these amendments. Support for the amendments to claim 31 is found in the claims as originally filed, and throughout the specification, in particular at the following locations: paragraphs 0031, 0035, 0094, and 0079-0082. Accordingly, no new matter is added by these amendments.

Claims 56, 63, and 65 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Status of Office Action

The Office Action dated July 18, 2008 indicates in the Summary and page 2 that it is non-final. However, at page 27 the Examiner includes language indicating that the Office Action is made final. Applicants respectfully request that the Examiner confirm that the Office Action is non-final in the next communication.

Objections to the claims

Claims 56, 60, 62, and 63 were objected to.

Claim 56

The Office Action stated that claim 56 has a typographical error in line 4.

Claim 56 is canceled without prejudice to renewal, thereby rendering this objection moot.

Claim 60

The Office Action stated that claim 60 is objected to because the claim recites RNA transcripts that have not been elected.

Applicants elected Invention I in response to the Restriction Requirement dated December 23, 2005. The December 23, 2005 Restriction Requirement further required election of one of the genes listed in claim 60.

Applicants note that MPEP §803.04 states:

> **>Polynucleotide molecules defined by their nucleic acid sequence (hereinafter "nucleotide sequences") that encode< different proteins are structurally distinct chemical compounds**. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121and 37 CFR 1.141 *et seq.* Nevertheless, to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the *>Director< has decided *sua sponte* to partially waive the requirements of 37 CFR 1.141 *et seq.* and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See *Examination of Patent Applications Containing Nucleotide Sequences,* 1192 O.G. 68 (November 19, 1996).
> It has been determined that **normally ten sequences constitute a reasonable number for examination purposes**. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction.
> (MPEP §803.04, emphasis added)

Without conceding as to the correctness of the objection to claim 60, and solely in the interest of expediting prosecution, claim 60 is amended to recite ErbB3, EREG, ID1, TITF1, CA9, CD44v6, DR5, KRT17, P14ARF, and PLAUR.

Claim 62

The Office Action stated that claim 62 is objected to for the recitation of "Kirt17"; and stated that the gene is called "KRT17."

Claim 62 is amended, as noted above, to change "Kirt17" to "KRT17."

Claim 63

The Office Action stated that claim 63 is objected to because of a typographical error in line 3. Claim 63 is canceled without prejudice to renewal, thereby rendering this objection moot.

Rejection under 35 U.S.C. §112, second paragraph

Claims 31, 35-38, 41-47, 51, 52, 55, 56, 59, 60, 62, 63, and 65 were rejected under 35 U.S.C. §112, second paragraphs, as allegedly indefinite. To the extent that the rejection may still apply to the amended claims, it is respectfully traversed.

Claims 56, 63, and 65 are canceled without prejudice to renewal, thereby rendering rejection of these claims moot.

The Office Action stated that claims 31, 35-38, 41-47, 51, 52, 59, 60, 62, and 63 are indefinite "because the claims to not clearly set forth a step of producing the likelihood that a human cancer patient will response to treatment with an ErbB1 inhibitor." (*See*, Office Action, page 5.)

Without conceding as to the correctness of this rejection, claim 31 is amended to recite a "predicting" step.

Conclusion as to the rejection under 35 U.S.C. §112, second paragraph

Applicants submit that the rejection of claims 31, 35-38, 41-47, 51, 52, 55, 59, 60, 62, 63, and 65 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §112, first paragraph

Claims 31, 35-38, 41-47, 51, 52, 56, 59, 60, 62, 63, and 65 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. To the extent that the rejection may still apply to the amended claims, it is respectfully traversed.

Claims 56, 63, and 65 are canceled without prejudice to renewal, thereby rendering rejection of these claims moot.

The Office Action stated that claim 31 is broad and encompasses a method wherein the inhibitor can be any inhibitor in the genus of ErbB1 inhibitors. (*See, e.g.*, Office Action, p. 8.) The Office Action stated that the term "response" could encompass any type of response. (*See, e.g.*, Office Action, p. 8.) The Office Action stated that the claim does not recite how one would use the LAMC2 level to make the prediction. (*See, e.g.*, Office Action, p. 9.) The Office Action stated that the claims encompass a method of determining the level of any LAMC2 transcript. (*See, e.g.*, Office Action, p. 9.)

Applicants respectfully traverse the rejection. Applicants' position on the enablement rejection has been made of record in the amendment, filed on April 17, 2008 and responsive to the Office Action dated October 19, 2007. The arguments made in the April 17, 2008 amendment need not be repeated in detail here.

"ErbB1 inhibitor"

Claim 31 currently recites that the ErbB1 inhibitor interacts with an ErbB1 receptor. Those skilled in the art as of the November 15, 2002 were aware of a number of ErbB1 inhibitors that interact with an ErbB1 receptor.

As discussed in the April 17, 2008 amendment, Applicants have presented data (e.g., Declaration of Joffre Baker; provided to the Office on December 21, 2006) showing that, in a study of patients treated with an EGFR inhibitor selected from erlotinib, gefitinib, cetuximab (which was inadvertently referred to in the Baker Declaration as "cytoximab"), EMD72000 (which was inadvertently referred to in the Baker Declaration as EMB72000), and AEE788, a correlation between response to treatment with EGFR inhibitor and LAMC2 levels was made. Dr. Baker stated that the data indicate that overexpression of LAMC2 in colon tumor tissue showed a negative (e.g., inverse) correlation with response to treatment with any of the EGFR inhibitors. The data were provided in Example 2 of the instant application.

Erlotinib (*N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy) quinazolin-4-amine; also known by its trade name Tarceva®) is a quinazoline compound that is an EGFR tyrosine kinase inhibitor. (*See*, Specification, paragraph 0082.)

Gefitinib (*N*-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine; also known as ZD1839 or Iressa) is another quinazoline compound that is an EGFR tyrosine kinase inhibitor. (*See*, Specification, paragraph 0079.)

Cetuximab (marketed under the name Erbitux) is a chimeric monoclonal antibody that is an EGFR inhibitor. (*See*, Specification, paragraph 0081.)

EMD72000 (also known as matuzumab) is a humanized anti-EGFR monoclonal antibody.

AEE788 is a 7H-pyrrolo[2,3-d] pyrimidine that is an EGFR inhibitor.

Thus, Applicants have shown a negative correlation between LAMC2 transcript levels and patient response to at least **three** classes of EGFR inhibitor, namely to:

1) EGFR inhibitors of the quinazoline class;

2) EGFR inhibitors of the monoclonal antibody class; and

3) EGFR inhibitors of the pyrrolopyrimidine class.

A number of ErbB1 inhibitor compounds of these and other classes were known in the art as of the November 15, 2002 priority date of the instant application; and the instant application lists several known ErbB1 inhibitors. Furthermore, it should be noted that ligand-bound ErbB1 acts by activating certain well-known signaling pathways. It has been shown amply in the literature that these signaling pathways can be disrupted by any of a wide variety of ErbB1 inhibitors of a number of different classes.

Nevertheless, and solely in the interest of expediting prosecution, claim 31 is amended to recite "wherein the ErbB1 inhibitor is erlotinib, cetuximab, or gefitinib."

"Response"

The Office Action stated that the term "response" is broad because it encompasses any type of response

However, as noted in the April 17, 2008 amendment, those in the field would understand that "response" to an ErbB1 inhibitor would refer to a response in terms of the cancer itself, e.g., decreased tumor load, reduction in cancer cell number, and the like. (*See, e.g.*, Specification at paragraphs [0035], [0094].)

Nevertheless, and solely in the interest of expediting prosecution, claim 31 is amended to recite "clinically beneficial patient response."

"LAMC2 transcript"

The Office Action stated that the claims "encompass a method of determining the level of ANY LAMC2 transcript." However, the Office Action did not elaborate on this comment.

It is Applicants' position that those skilled in the art as of the November 15, 2002 priority date could readily practice the instant methods as claimed without undue experimentation. Those skilled in the art, as of the November 15, 2002 priority date, could readily assay a normalized level of a LAMC2 transcript in a sample comprising ErbB1-expressing colon cancer cells.

Additional comments

The Office Action stated that the claim does not recite how one would use the LAMC2 level to make the prediction. However, as discussed in the April 17, 2008 amendment, Applicants have provided ample guidance in the specification that indicates that there is an inverse correlation between response of a patient to treatment with an EGFR (ErbB1) inhibitor and LAMC2 transcript levels. The data indicate that overexpression of LAMC2 in colon tumor tissue showed a negative correlation with response to treatment with any of the ErbB1 inhibitors. The data were provided in Example 2 of the instant application. The specification describes how the levels of gene expression were measured, normalized, and evaluated. (*See, e.g.*, Specification, paragraph 0095.)

Given the guidance in the specification, including working examples, and the knowledge and skill level in the art, those skilled in the art would be able to carry out the claimed method without undue experimentation.

The Office Action stated that the instant specification does not teach which ErbB1 inhibitors were used in Examples 1 and 2. (*See* Office Action, p. 12.) However, as discussed in the April 17, 2008 amendment, the specification describes a number of ErbB1 inhibitors. As noted above, and as discussed in the April 17, 2008 amendment, Applicants have presented data showing an inverse correlation between patient response to a number of ErbB1 inhibitors of various classes and normalized LAMC2 transcript levels. As such, those skilled in the art would find it reasonable to expect that an inverse correlation between patient response to other ErbB1 inhibitors and normalized LAMC2 levels would also be observed. The Office Action has not presented sufficient rationale as to why one would doubt

that an inverse correlation between patient response to any of a variety of ErbB1 inhibitors and normalized LAMC2 levels would be observed.[1]

The Office Action cited various publications to support its assertions. However, as discussed in the April 17, 2008 response, the publications cited in the Office Action do not support a conclusion that the instant claims are not enabled.

Conclusion as to the rejection under 35 U.S.C. §112, first paragraph

Applicants submit that the rejection of claims 31, 35-38, 41-47, 51, 52, 56, 59, 60, 62, 63, and 65 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §102(b)

Claims 31, 35-37, 56, 63, and 65 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Hlubek ((2001) *Cancer Res.* 61:8089 ("Hlubek") "as evidenced by Salomon" ((1995) *Crit. Rev. Oncol/Hematol.* 19:183 ("Salomon"). To the extent that the rejection may still apply to the amended claims, it is respectfully traversed.

Claims 56, 63, and 65 are canceled without prejudice to renewal, thereby rendering this rejection of claims 56, 63, and 65 moot.

The Office Action stated that Hlubek teaches a method comprising determining the expression levels of LAMC2 in cells obtained from patients with colorectal carcinomas; and that Salomon teaches that ~25-77% of colon cancer patients studied have ErbB1 expressing cancer cells. The Office Action stated that Hlubek thus teaches a method comprising (a) assaying the LAMC2 transcript in a sample comprising ErbB1 expressing cancer cells; and (b) analyzing the LAMC2 transcript. (*See* Office Action, p. 20, 21.)

As noted above, amended claim 31 recites a "predicting" step.

[1] *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

As the Examiner acknowledges, Hlubek neither discloses nor suggests a method of predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor, the method comprising determining the normalized level of a LAMC2 transcript, analyzing the normalized level of the LAMC2 transcript, and predicting the likelihood of response, as recited in amended claim 31. (*See* Office Action, p. 27.) Therefore the rejection is unsupported by the art and should be withdrawn.

Conclusion as to the rejection under 35 U.S.C. §102(b)

In view of the above, Applicants respectfully assert that the Examiner's assertions do not support a rejection of independent claim 31 under 35 U.S.C. § 102(b). Claims 35-37 depend directly from independent claim 31, and are thus patentable for at least the same reasons. Applicants submit that the rejection of claims 31, 35-37, 56, 63, and 65 under 35 U.S.C. §102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejections under 35 U.S.C. §103(a)

Claim 38 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hlubek, as evidenced by Salomon, in view of Comite, U.S. Patent Publication No. 2002/0194002 ("Comite"). Claims 41-47, 52, and 59 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hlubek, as evidenced by Salomon, in view of Bao, U.S. Patent No. 6,251,601 ("Bao"). Claim 51 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hlubek, as evidence by Salomon, in view of Lehman and Kreipe, (2001) *Methods* 25:409 ("Lehman"). Claim 60 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hlubek, as evidenced by Salomon, in view of Chun, (2000) *J. Korean Med. Sci.* 61:808 ("Chun"). Claim 62 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hlubek, as evidence by Salomon, in view of Notterman et al., (2001) *Cancer Res.* 61:3124 ("Notterman"). To the extent that the rejections may still apply to the amended claims, they are respectfully traversed.

Claim 56 is canceled without prejudice to renewal, thereby rendering this rejection of claim 56 moot.

As noted above, amended claim 31 recites a "predicting" step.

Hlubek neither discloses nor suggests a method of predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor, the method comprising determining the normalized level of a LAMC2 transcript, analyzing the normalized level of the LAMC2 transcript, and predicting the likelihood of response, as recited in amended claim 31.

Nor do the cited secondary references cure the deficiency of Hlubek. None of the cited secondary references disclose or suggest a method of predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor, the method comprising determining the normalized level of a LAMC2 transcript, analyzing the normalized level of the LAMC2 transcript, and predicting the likelihood of response. Therefore, Hlubek, whether viewed separately or in combination with any of the secondary references, cannot render amended claim 31obvious.

Conclusion as to the rejections under 35 U.S.C. §103(a)

As described above, Hlubek fails to teach or suggest each and every element of independent claim 31, upon which claims 38, 41-47, 51, 52, 59, 60, and 62 depend. Moreover, the secondary references cited by the Examiner fail to teach what Hlubek lacks. Therefore, the cited art does not support the rejections of claims 38, 41-47, 51, 52, 59, 60, and 62 under 35 U.S.C. §103(a).

Applicants submit that the rejections under 35 U.S.C. §103(a) have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GHDX-005.

Respectfully submitted,
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Date: October 17, 2008

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